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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAVIGLIANITI, ANTHONY JOSEPH	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 04/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/765,227	KUKI ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 13 and 15-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 and 14 is/are rejected.

7)☒ Claim(s) 5-12 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 – 23 are currently pending in the application.

Priority

The Specification claims priority to Provisional Application No. 60/443,223, filed January 27, 2003. Please amend the Application Data Sheet to reflect the Provisional Application serial number and filing date.

Information Disclosure Statement

The Information Disclosure Statements filed on May 7, 2004, June 11, 2004, and November 2, 2004, are hereby acknowledged and were considered by the examiner.

Election/Restrictions

The Markush groups set forth in the claims include both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. **For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. 121,** wherein an Invention is a set of patentably distinct inventions of a broad statutory category (e.g., compounds, methods of use, methods of making, etc.):

I. **Claims 1 – 12**, and **14**, drawn to chemical compounds and compositions of Formula (I), classified in class 546, subclass 87, and other subclasses.

II. **Claims 13** and **15**, drawn to chemical compounds and compositions of Formula (Ib), classified in class 546, subclass 64, and other subclasses.

III. **Claims 16 – 23**, drawn to methods of inhibiting the activity of HIV integrase enzyme or inhibiting replication of HIV or methods of treating a disease mediated by HIV using compounds and compositions of Formula (I) or (Ib), classified in class 514, subclasses 293, 287, 212.06, and other subclasses.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. §121 as follows:

In accordance with the decisions in In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980) and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App & Int. 1984), restriction of a Markush group is proper where the compounds with the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member(s).

If **Group I or Group II** is elected, **an election of a single compound is further required**, including an exact definition of each substitution on the base molecule, where a single member at each substituent group is selected. If the base molecule has variable groups $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$ $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and **n**, where, for example, $\mathbf{R^7}$ is recited to represent:

> "...$C_1 - C_6$ alkyl, $C_2 - C_6$ alkenyl, or $C_2 - C_6$ alkynyl, all of which are optionally substituted by one or more substituents independently selected from halogen, $C_1 - C_6$ alkyl, $C_2 - C_6$ alkenyl, $C_2 - C_6$ alkynyl, aryl, cycloalkyl, heterocycloalkyl, and heteroaryl, wherein said aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more substituents independently selected from halogen, $C_1 - C_6$ alkyl, $C_2 - C_6$ alkenyl, and $C_2 - C_6$ alkynyl..."

then Applicant must select a single substituent representing $\mathbf{R}^7$, such as "fluorobenzyl," and so on, such that there are specific values representing each subsequent variable position, so that a single compound is identified. One suggestion for the election of a single compound is to select one of the compounds in Examples 1 – 13 in the Specification at pp. 37 - 44.

In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim which fall into the same class and subclass as the elected compound, but may also include additional compounds which fall in related subclasses.

Examination will then proceed on the elected compound *and* the entire scope of the invention encompassing the elected compound as defined by common classification. A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits.

Note that the restriction requirement will not be made final until such time as Applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making the compounds under investigation. This will be set forth by reference to specific class(es) and subclass(es) examined.

Should Applicant traverse on the ground that the compounds are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either

instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103(a) of the other invention.

All compounds falling outside of the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to non-elected subject matter and will be withdrawn from consideration under 35 U.S.C. §121 and 37 C.F.R. §1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. §121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(i).

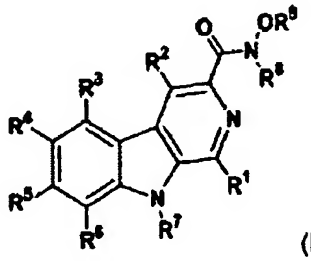
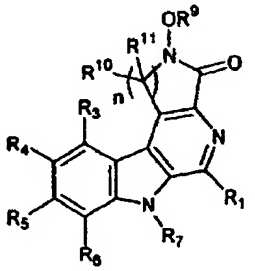
If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can set forth a group of compounds which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP §608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical

structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP §806.04, MPEP §808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group); i.e., they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other, because of the following reasons:

Group I and **Group II** are related as products which are distinct inventions because they represented by Markush groups  (I) and  (Ib), respectively. **Group I** contains compounds with a tricyclic core structure with two heterocyclic rings, while **Group II** contains compounds with a tetracyclic core structure with three heterocyclic rings, and have separate patent classifications. A compound found to anticipate

Group I in the prior art would not anticipate or render obvious a compound from **Group II**, and the inventions are distinct from each other.

Group I and **Group III** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially-different process of using that product. See MPEP §806.05(h). Applying this rule to the instant case, a method of inhibiting replication of HIV in a mammal (e.g., **Claim 20** in **Group III**) can be practiced with other, materially-different products, such as saquinavir, zidovudine, and zalcitabine. See, e.g., A. Collier, et al., "Treatment of Human Immunodeficiency Virus Infection with Saquinavir, Zidovudine, and Zalcitabine," N. Engl. J. Med., vol. 334(16), pages 1011 – 1017, at p. 1015, col. 1, lines 33 – 36. These two inventions are therefore distinct from one another.

Group II and **Group III** are also related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially-different process of using that product. See MPEP §806.05(h). As before, a method of inhibiting replication of HIV in a mammal (e.g., **Claim 20** in **Group III**) can be practiced with other, materially-different products, such as saquinavir, zidovudine, and zalcitabine. See, e.g., A. Collier, et al., "Treatment of Human Immunodeficiency Virus Infection with Saquinavir, Zidovudine, and Zalcitabine," N. Engl. J. Med., vol. 334(16), pages 1011 – 1017, at p. 1015, col. 1, lines 33 – 36. These two inventions are also distinct from one another.

In addition, because of the plethora of classes and subclasses in each of the Groups, a serious burden is imposed upon the examiner to perform a complete search of the defined areas. Therefore, for the reasons given above, the restriction set forth is proper, and not to restrict would impose a serious burden in the examination of this application.

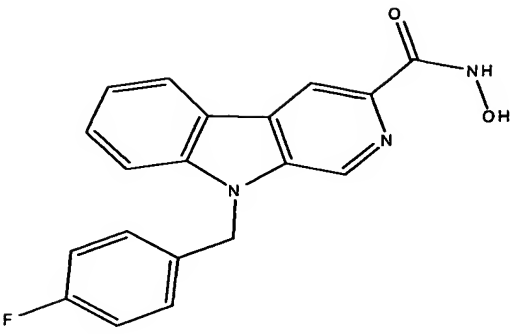
Advisory of Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Election by Applicant:

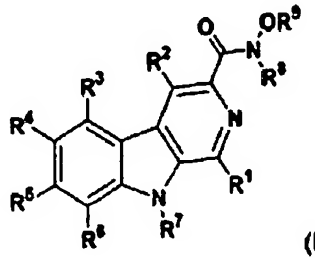
During a telephone conversation with Jeff Tidwell, Esq., on February 25, 2005, the above restriction requirements were discussed, and **an election was made, without traverse, of Group I, and an election of the compound 9-(4-fluorobenzyl)-N-hydroxy-9H-β-carboline-3-**

carboxamide, with the structure:  (Example 1, p. 37 of the Specification).

Applicant is advised that the reply to this requirement to be complete must include an election of the Invention to be examined even though the requirement be traversed. 37 C.F.R. §1.143. Applicant is further advised that a reply to this requirement must include an identification of the specific compound that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Claims 13, 15, and 16 – 23 were withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

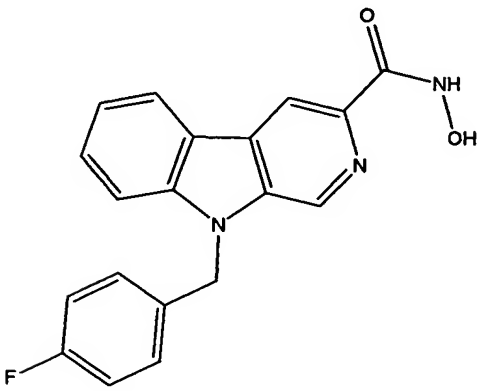
Analysis of Claims 1 – 12 and 14 (Prior Art Searched)

The present invention claims compounds of Formula (I):  (I),

where $\mathbf{R^7}$ is $C_1 - C_6$ alkyl, alkenyl, alkynyl (optionally substituted), but all other **R** groups shown may be, *inter alia,* a hydrogen atom. The invention was searched as follows:

Elected Compound

The **elected compound**, 9-(4-fluorobenzyl)-N-hydroxy-9H-β-carboline-3-carboxamide,

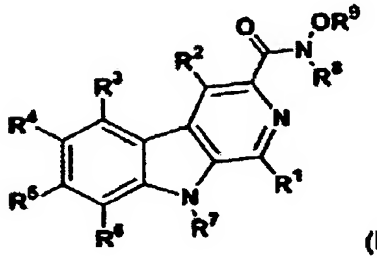


(Example 1, p. 37 of the Specification), was searched and appears to be free of the prior art of record.

Expansion of search to related compounds within same patent classification as the invention

The search of the prior art was expanded to include compounds in the same patent classification and subclassification group as the elected species.

Specifically, the search of the prior art included all β-carboline compounds of Formula (I),



(I), substituted at the 3-position with an hydroxamic acid group C(=O)NR^8OR^9, and where R^1, R^2, R^3, R^4, R^5, R^6 were hydrogen, halogen, C_1-C_6 alkyl, alkoxy C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, OR_c, $-NO_2$, and $N(R_c)_2$, where R_c was hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl group; R^7 was C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, optionally substituted by halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, aryl, cycloaryl wherein the aryl or cycloaryl group was optionally substituted with

halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl groups; and $\mathbf{R^8}$ and $\mathbf{R^9}$ were hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, optionally substituted by halogen, aryl, or cycloaryl wherein the aryl or cycloaryl group was optionally substituted with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl groups.

NOTE: The search of prior art did *not* include compounds which were outside of the general patent classification areas of the elected invention. Specifically, the search of the prior art did not encompass compounds where $\mathbf{R^7}$ was an C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl group *optionally substituted by a heterocycloalkyl or heteroaryl group*, and where $\mathbf{R^8}$ and $\mathbf{R^9}$ were alkyl, alkenyl, or alkynyl groups *optionally substituted by a heterocycloalkyl and heteroaryl group.*

As described below, it was during the expansion of the search beyond the elected compound that prior art was found which formed the basis for the rejection below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

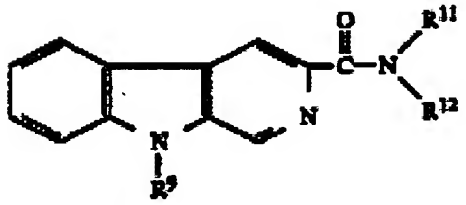
The Graham factors for the present invention are analyzed below.

Claims 1, 2, 3, 4 and 14:

Claims 1, 2, 3, 4 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,010,077 (issued April 23, 1991) to Claus Braestrup, et al., further in view of the teaching by Beng Ho, et al., "Inhibitors of Monoamine Oxidase: Influence of Methyl Substitution on the Inhibitory Activity of β-Carbolines," J. Pharmaceutical Sciences, vol. 57, pages 269 - 274 (1968).

Determining the scope and contents of the prior art

U.S. Patent 5,010,077 (Braestrup) taught β-Carboline derivatives of structure



at col. 21, line 2, including a specific embodiment at col. 21, line 16 (Table III) where $\mathbf{R^{11}}$ was H, $\mathbf{R^{12}}$ was –OH, and where $\mathbf{R^9}$ was H, which yielded a compound with a melting point of 237.5° – 239° C. See also Braestrup, col. 35, lines 53 – 55 (claim 3) which overlaps the same set of compounds as the structure shown above.

Although the Braestrup patent defined substituent $\mathbf{R^9}$ as "hydrogen, $C_{1\text{-}8}$ *alkyl*, $C_{1\text{-}8}$ alkenyl, $C_{1\text{-}8}$-alkoxycarbonyl, $C_{1\text{-}8}$-alkenyloxycarbonyl, or $C_{1\text{-}8}$-alkenyloxy," [emphasis added] in the Abstract and Specification, Braestrup provided no specific embodiments of his invention where the substituent on the indolic nitrogen atom (i.e., $\mathbf{R^9}$) was "$C_1 - C_8$ alkyl," which would

have anticipated all the limitations of the present invention. Instead, Braestrup's preferred examples and his claims have only "hydrogen" for $\mathbf{R^9}$.

The Braestrup patent also claimed the "pharmaceutical compositions" of these compounds, which is germane to **Claim 14** of the present invention. See Braestrup at col. 36, lines 17 – 18 (Claim 5).

Beng Ho's series of three articles in the Journal of Pharmaceutical Sciences taught that β-carboline compounds with a methyl-for-hydrogen substitution at the 9-position of the ring (the indole-N) demonstrated a significant increase in enzymatic inhibitory activity (15-fold for the tetrahydro-β-carboline derivative, and 3-fold for the aromatic β-carboline derivative), which was attributed to the electron donor properties of the methyl group and the increase in hydrophobicity at that site. See Ho at page 270, Table II (compounds XX and XXIII) and col. 2, lines 1 – 3.

Ascertaining the differences between the prior art and the claims at issue

The Braestrup patent discloses the limitations of **Claims 1, 2, 3, and 4** of the present invention, except for the requirement that the substituent at the 9-position on the β-carboline ring (i.e., $\mathbf{R^7}$) must be $C_1 - C_6$ alkyl, alkenyl or alkynyl (optionally substituted) while Braestrup only discloses examples with hydrogen at that site.

Although it is well-established that the substitution of methyl-for-hydrogen on a known compound, generally, is not a patentable modification absent unexpected or unobvious results (see, e.g., In re Wood, 582 F.2d 638, 199 USPQ 137 (CCPA 1978), where the substitution of two methyl groups for two hydrogen atoms on a heterocyclic [dihydropteridine] ring was *prima facie* obvious), the examiner for the instant application sought a reference showing the effect of methyl-for-hydrogen substitution at the 9-position of a β-carboline ring. The series of articles by

Beng Ho in the Journal of Pharmaceutical Sciences in the late 1960's taught that substitution of methyl-for-hydrogen at the 9-position of the β-carboline ring improved its inhibition of certain enzymes with hydrophobic binding sites (in that instance, the enzyme was monoamine oxidase). However, the substituted β-carboline compounds taught in Ho are different than those in the present invention in that the prior art does not disclose a hydroxamic acid substituent at the 3-position of the β-carboline ring.

Another difference is that the β-carboline derivatives in the present invention are used for inhibition of the enzyme "HIV-integrase," while the β-carboline derivatives of the prior art were used as pharmaceuticals "acting on the central nervous system" (Braestrup) and as "inhibitors of the enzyme monoamine oxidase" (Ho). However, this claims at issue do not disclose an intended use, but rather just compounds and compositions of Formula (I), so this difference does not affect the analysis.

Resolving the level of ordinary skill in the pertinent art

At the time of this application, the β-carboline-3-hydroxamic acid compounds (and the corresponding "pharmaceutical compositions") of the present invention would have been obvious to a person of skill in the art because of the compounds disclosed by Braestrup in U.S Patent 5,010,077, in light of the established case law on "methyl-for-hydrogen" substitution and because of the teaching of Ho. The skilled artisan would have been motivated to select the "methyl-for-hydrogen" substitution at the 9-position of the β-carboline ring for the compounds taught by Braestrup because Ho had previously demonstrated that introduction of a methyl group in lieu of hydrogen on the indolic nitrogen of a β-carboline compound increased its enzyme inhibitory activity three-fold, albeit in a different enzyme. Ho taught that this increased

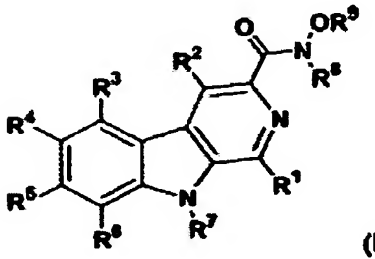
inhibitory activity was probably due to the electron-donating property of the methyl group, or due to the methyl group itself making the β-carboline derivative more hydrophobic (thereby increasing its affinity for the hydrophobic binding site on the enzyme). See Ho, et al., J. Pharm. Sci., vol. 58(2), pages 219 – 221 (Feb. 1969), at p. 219, lines 1 – 8. Thus the skilled artisan would have had a reasonable expectation of success in improving enzyme inhibitory activity (particularly where the enzyme binding site was hydrophobic) by making the "methyl-for-hydrogen" substitution at the 9-position of the β-carboline ring for the compounds disclosed by Braestrup.

For the same reasons that the compounds in **Claims 1 – 4** of the present invention were rendered obvious by the prior art, so too would the "pharmaceutical composition" in **Claim 14** of the present invention have been rendered obvious by the same references. See Braestrup at col. 36, lines 17 – 18 (Claim 5: "pharmaceutical composition").

As noted before, even though the "intended use" for the compounds are different between the present invention and the prior art references, the claims at issue for this analysis are simply for the compounds (and compositions) of Formula (I) themselves.

Other relevant prior art not supporting separate rejections under 35 U.S.C. §103

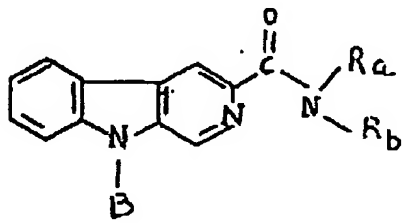
As noted earlier, the present (elected) invention claims compounds of Formula (I),



(I), which are β-carboline compounds substituted at the 3-

position with an hydroxamic acid group [C(=O)NR^8OR^9], at the 9-position with an optionally-substituted alkyl group, etc. (i.e., not hydrogen).

Relevant prior art which was close to the present invention was found in UK Patent Application 2 209 032 A (published April 26, 1989 and cited by the applicant on the Form 1449 disclosure) by Charles Hedgecock and Colin Gardner, which claimed compounds of structure:



, where R_a is alkyl and R_b is alkoxy, and **B** is defined only as "protecting group" (Claim 13, page 20, lines 18 – 33). UK Patent Application 2 209 032 A described compounds which anticipated all of the limitations of the present generic invention (i.e., where R^1, R^2, R^3, R^4, R^5, R^6, R^6, R^8, and R^9 in the present invention are all hydrogen atoms) *except for* the substituent at the 9-position of the β-carboline ring. The present invention requires the substituent at the 9-position (i.e., R^7) to be an optionally substituted alkyl, alkenyl, or alkynyl group; by contrast, the only "preferred" value for **B** (protecting group) disclosed in UK Patent Application 2 209 032 A was "p-toluenesulphonyl" (Specification at page 3. line 23: "**B** represents an appropriate protecting group, for example, a paratoluenesulphonyl group"; or page 6, line 18, "...protecting group **B**, for example, paratoluenesulfonyl chloride"). Even though the range of values for R^7 in the present invention could be manipulated to be a large ring system that could be characterized as a "protecting group," there was no indication in the present invention that the substituent at R^7 was intended to serve as a "protecting group," and thus there would have been insufficient motivation for a person of skill in the at the time of the application

to have selected a value for "**B**" that read on all of the limitations of the present invention. However, this prior art is included as guidance for the applicant if the claims are amended.

In view of the expanded search noted above, **Claims 5, 6, 7, 8, 9, 10, 11,** and **12** of the present invention appear to be free of the prior art of record (these claims are, however, the subject of an objection, described below). In particular, the limitations of these claims by the substituent at the 9-position of the β-carboline ring (i.e., $\mathbf{R^7}$ is an optionally-substituted benzyl group) are sufficient to avoid the prior art of record.

The objections pursuant to 35 U.S.C. §103 would be obviated by amending **Claim 1** and **Claim 3** so that $\mathbf{R^7}$ would not read on a β-carboline-3-hydroxamic acid compound with a "methyl" group at the 9-position of the ring (i.e., the indolic nitrogen atom).

Please note also that the expansion of the search of the prior art included all claimed values for $\mathbf{R^7}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ except where the secondary substituent was a "heterocycloalkyl" or "heteroaryl" group, as described in detail above.

Claim Objections

Claims 5 – 12 are objected to as being dependent upon a rejected base claim, but appear to be free of the art if rewritten in independent form including all of the limitations of the base claim and any intervening claims. See MPEP §608.01(n)(V).

Conclusion

Claims 1, 2, 3, 4 and **14** are rejected pursuant to 35 U.S.C. §103.

Claims 5 – 12 are objected to as being dependent upon a rejected base claim.

Claims 13 and **15 – 23** were withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, may be reached at (571) 272-0699.

The FAX phone number for the organization where this application or proceeding is assigned is (571) 273-8300. **Please note that this is a new central FAX number for all official correspondence.**

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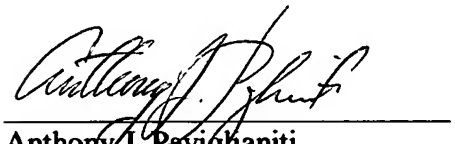

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